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Clinical Focus

Primary Progressive Apraxia of Speech: Clinical Features and Acoustic and Neurologic Correlates

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Purpose: This study summarizes 2 illustrative cases of a neurodegenerative speech disorder, primary progressive apraxia of speech (AOS), as a vehicle for providing an overview of the disorder and an approach to describing and quantifying its perceptual features and some of its temporal acoustic attributes.
Method: Two individuals with primary progressive AOS underwent speech-language and neurologic evaluations on 2 occasions, ranging from 2.0 to 7.5 years postonset. Performance on several tests, tasks, and rating scales, as well as several acoustic measures, were compared over time within and between cases. Acoustic measures were compared with performance of control speakers.
Results: Both patients initially presented with AOS as the only or predominant sign of disease and without aphasia or dysarthria. The presenting features and temporal progression were captured in an AOS Rating Scale, an Articulation Error Score, and temporal acoustic measures of utterance duration, syllable rates per second, rates of speechlike alternating motion and sequential motion, and a pairwise variability index measure.
Conclusions: AOS can be the predominant manifestation of neurodegenerative disease. Clinical ratings of its attributes and acoustic measures of some of its temporal characteristics can support its diagnosis and help quantify its salient characteristics and progression over time.

For the past half century, *acquired apraxia of speech* (AOS)—a disorder of motor speech planning and programming—has been the subject of considerable research regarding its underlying nature, localization, defining diagnostic characteristics, and clinical management. It has earned this attention at least partly because it (a) represents a unique, "higher level" motor speech disorder, (b) occasionally manifests without other speech or language deficits, (c) is conceptually sandwiched between more frequently occurring and often co-occurring aphasia and dysarthria, and (d) seems to require an approach to treatment that differs in several ways from other communication disorders. These attributes invite careful clinical study with definitional and diagnostic specificity. Critical reviews have recognized progress as well as persisting gaps in our understanding of the disorder (McNeil, Robin, & Schmidt, 2009; Wambaugh, Duffy, McNeil, Robin, & Rogers, 2006; Ziegler, Aichert, & Staiger, 2012).

Stroke is the most frequent cause of AOS in most research studies and almost certainly in most clinical settings (Duffy, 2013; Wambaugh et al., 2006); it is thus the source of most of what we understand about the disorder. Most other etiologies (e.g., neurosurgery, traumatic brain injury) share with stroke the possibility of improvement or an eventual stable degree of impairment. However, in the last few decades a number of case studies and case series have documented the presence of AOS in neurodegenerative disease, often as part of the neurodegenerative syndrome of primary progressive aphasia (PPA) but sometimes in the absence of other neurological deficits, including aphasia or other neurodegenerative communication disorders (e.g., Ackermann, Scharf, Hertrich, & Daum, 1997; Croot, Ballard, Leyton, & Hodges, 2012; Didic, Ceccaldi, & Poncet, 1998; Duffy, 2006; Josephs et al., 2005, 2006, 2010, 2012, 2013; Laganaro, Croisier, Bagou, & Assal, 2012; Ricci et al., 2008). Neurodegenerative AOS is the focus of this article.

The understanding and diagnosis of neurodegenerative AOS is often difficult to separate from definitions and classifications of PPA. Current consensus criteria for the clinical diagnosis of PPA (Gorno-Tempini et al., 2011) identify

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two core features associated with the agrammatic variant of PPA, only one of which must be present for the diagnosis: (a) agrammatism in spoken or written language production and (b) AOS. Thus, the criteria permit a diagnosis of agrammatic aphasia in someone with only AOS and no evidence of agrammatism in expressive language or difficulty with comprehension of syntactically complex sentences, as long as single-word comprehension and object knowledge are spared. As a result, some people can receive a diagnosis of PPA when they have no aphasia and when the more appropriate diagnosis would be progressive AOS. This may lead to underestimation of the frequency of neurodegenerative AOS because it can be buried under the diagnostic heading of PPA (see Duffy & McNeil, 2008, and Josephs et al., 2012, 2013, 2014, for more detailed discussions of these diagnostic criteria issues and the rationale for not diagnosing PPA when AOS is the only speech-language impairment).

A recent review of studies of the agrammatic variant of PPA, or PPA unspecified as to type, noted a median AOS prevalence of 78% across 162 aggregated cases (Duffy, Strand, & Josephs, 2014). The severity of AOS in individual cases sometimes exceeded that of the aphasia, and in about 20% of cases AOS was the primary and sometimes only deficit (i.e., there was little or no evidence of aphasia). When AOS was the only or the primary neurological deficit, it has been referred to as primary progressive apraxia of speech (PPAOS; Duffy, 2006; Duffy & McNeil, 2008; Josephs et al., 2012, 2013). In such patients, there is also converging imaging and pathologic evidence that supports the distinction of PPAOS from PPA. That is, various neuroimaging modalities (voxel-based morphometry, diffusion tensor imaging analysis, positron emission tomography) suggest that the superior lateral premotor and supplementary motor cortices are the main cortical areas involved in PPAOS, with white matter involvement in similar areas but also extending into the inferior premotor cortex, body of the corpus callosum, and superior longitudinal fasciculus (Josephs et al., 2012). These loci differ from that observed in people with the agrammatic variant of PPA without AOS or with AOS less severe than aphasia, in which there is more widespread involvement that includes the premotor and prefrontal cortex, temporal and parietal lobes, caudate nucleus, and insula (Josephs et al., 2013). Furthermore, when AOS is present, with or without aphasia, the most frequent pathological diagnoses at autopsy are progressive supranuclear palsy or corticobasal degeneration, both of which are consistent with underlying tau pathology (Deramecourt et al., 2010; Josephs et al., 2006, 2012). In contrast, limited data suggest that the agrammatic variant of PPA without AOS is associated with TDP-43–positive frontotemporal lobar degeneration pathology (Deramecourt et al., 2010).

Study of progressive AOS may contribute to our understanding of AOS in general and might reveal features of the disorder that have not been associated with stroke-related AOS because progressive AOS reflects the gradual dissolution of speech motor programming in brain regions that might differ from those affected when stroke is the etiology (Duffy & Josephs, 2012; Laganaro et al., 2012). Although stroke-related AOS versus neurodegenerative AOS should share many clinical features, any reliable differences, if they exist, may help establish etiology and further delineate the anatomic components of the speech programming network.

In spite of now-numerous reports of progressive AOS, only a few have described its features in cases without aphasia (Josephs et al., 2006, 2010, 2012; Laganaro et al., 2012). In addition, although it has been argued that acoustic measures may aid the diagnostic reliability and quantification of AOS in general (Haley, Jacks, de Riesthal, Abou-Khlil, & Roth, 2012), the acoustic correlates of progressive AOS have received limited attention. Measures of temporal aspects of speech in PPA, in which AOS was present in at least some participants, have been crude (e.g., duration of narratives) and have been confounded by co-occurring aphasia (Ash et al., 2009; Code, Ball, Tree, & Dawe, 2013; Knibb, Woollams, Hodges, & Patterson, 2009). In addition, only two single-case reports of individuals with PPA and AOS have presented longitudinal data about changes in speech rate (Ackermann et al., 1997; Code et al., 2013).

Although only a single-case report has measured temporal aspects of speech production in people with PPAOS (Laganaro et al., 2012), it has been shown that some acoustic measures differentiate patients with aphasia from those with aphasia plus AOS due to stroke (e.g., Rogers, 1997; Vergis et al., 2014) and distinguish among subtypes of PPA (Ballard et al., 2014). Most pertinent to the current study, Ballard et al. (2014) found that a measure of relative vowel duration differentiated patients with the agrammatic variant of PPA (70% of whom had AOS) from control subjects and patients with the logopenic variant of PPA and that the acoustic distinctions were in agreement with the clinical distinctions made by expert judges. The acoustic measures also correlated with neuroimaging abnormalities in areas associated with speech planning and programming. Acoustic measures also have potential value for indexing longitudinal changes in PPAOS (Laganaro et al., 2012).

In this article, we detail the speech-language and other neurological findings for two individuals with PPAOS at two points during their disease course, with emphasis on the clinical features of their AOS and some of its temporal acoustic characteristics and neurological correlates. The goals are (a) to familiarize clinicians with PPAOS as a clinical entity whose recognition is important to neurologic localization, diagnosis, prognosis, and management and to a more complete understanding of AOS in general, (b) to describe the salient speech-language and other neurological findings and changes that occurred over time, and (c) to illustrate an approach to describing and quantifying its perceptual features, including some easily measured temporal acoustic attributes that distinguish PPAOS from normal speech and that may be sensitive to change over time.

Method

Participants

The individuals described here, who will be referred to as AOS1 and AOS2, are fairly representative of patients

with PPAOS whom we have seen as part of an institutional review board–approved National Institutes of Health–funded study of neurodegenerative aphasia and AOS. They were selected because (a) the severity of their AOS during their initial assessment was similar, (b) the perceptual and acoustic features of their AOS contained similarities as well as differences, and (c) they were among a small number of patients we have seen for follow-up one year or longer following their initial evaluation, permitting insight into the evolution of their condition. A full description of these patients will be provided in the Results section. Control participants for acoustic analysis comparisons will be described under the Acoustic Analysis subheading.

Clinical Assessment

The two cases were assessed using several tests and tasks. Language measures reported here included the Western Aphasia Battery (WAB, Revised, Part 1; Kertesz, 2007), which assesses spontaneous speech, auditory verbal comprehension, repetition, and naming/word finding and provides an overall index of aphasia severity (Aphasia Quotient or AQ); the Writing Output subtest of the WAB (Part 2) as a measure of written narrative language; the Token Test, Part V (De Renzi & Vignolo, 1962) as a sensitive measure of spoken language comprehension; and a 15-item version of the Boston Naming Test (Lansing, Ivnik, Cullum, & Randolph, 1999) as a measure of picture naming ability.

Perceptual ratings of speech included:

1. The Apraxia of Speech Rating Scale (ASRS), a measure that has been useful in studies of progressive AOS (e.g., Josephs et al., 2012, 2013). It provides a quantitative description of the presence and prominence of 16 speech characteristics associated with AOS, with scores that can range from 0 to 64 (0 = *no abnormal speech characteristics*). Scores above 8 are consistent with clinical diagnoses of AOS (Strand, Duffy, Clark, & Josephs, 2014); the average ASRS score in people with progressive AOS is about 17 (interquartile range = 12.8 to 20.3; Josephs et al., 2013).
2. Two 5-point (0 = *normal*, 4 = *severe*) clinical rating scales of severity, one for AOS and the other for dysarthria.
3. A 10-point functional speech severity rating (MSD Severity), adapted from Yorkston, Strand, Miller, and Hillel (1993), where 1 = *nonvocal* and 10 = *normal speech*.

The above ratings were based on speech responses during conversation, WAB speech subtests, and supplementary speech tasks (see Appendix). Supplementary speech tasks included a maximum vowel prolongation, speechlike alternating motion rates (AMRs), speechlike sequential motion rates (SMRs), three sentences with a total of 17 words that contained several multisyllabic words, and three repetitions each of 13 mostly multisyllabic words.

4. Finally, a simple Articulation Error Score was derived from the percentage of 56 words on the supplementary speech tasks (i.e., three repetitions of 13 words plus one repetition of three sentences) in which any of the following characteristics were noted: distorted or undistorted sound substitutions, additions, or repetitions; sound omissions; sound prolongations (beyond those consistent with overall speech rate); false starts; and successful or unsuccessful attempts to correct sound errors. This error score may underestimate total errors within and across words because a word scored as an error might contain more than one error. Although the Articulation Error Score can reflect apraxic or phonological errors, for the two cases presented here the errors were judged as exclusively or predominantly apraxic in nature because they were nearly always distorted and associated with abnormal prosodic features not typically associated with phonological errors.

Because nonverbal oral apraxia can co-occur with PPAOS and PPA, an eight-item measure of nonverbal oral apraxia, with a maximum/best score of 32, was also administered (see Botha et al., 2014, for task description, scoring, and supporting data). The test scores and ratings for the two individuals are summarized in Tables 1 and 2.

Reliability of clinical judgments. On the basis of direct assessment or review of audio/video recordings, two of the authors (J.R.D., E.A.S.) independently agreed about the presence and severity of aphasia, AOS, dysarthria, and nonverbal oral apraxia for both cases at both points in time. Three of the authors (J.R.D., E.A.S., H.C.) also independently reviewed recordings of speech responses several months to 2 years after the initial assessment to score/rescore the ASRS and to make a judgment about the presence and type of dysarthria, if present, for both individuals on both test occasions. All agreed that AOS was present in both patients at both test times. Composite agreement among the three judges about the presence versus absence of each of the 16 rated features on the ASRS was 94% for AOS1 and 90% for AOS2; composite agreement within 1 point on the 5-point rating scale for the 16 features was 93% for AOS1 and 92% for AOS2. Two of the three judges agreed that dysarthria was not present during initial assessment of AOS1 (one judge felt mild ataxic dysarthria was present); two judges felt spastic dysarthria was present or equivocally present during the second assessment (one judge did not feel dysarthria was present). For AOS2, all three judges agreed dysarthria was not present during initial assessment and was equivocally present during the second assessment. All three agreed that, for both cases, any dysarthria was clearly less severe than the AOS. After discussion, the consensus conclusion was that dysarthria was not present in either case during their first assessment and that spastic dysarthria was equivocally present in both cases during the second assessment, primarily on the basis of mild or equivocal strained voice quality in both cases.

There was independent agreement that neither patient had aphasia during their initial assessment. There was independent agreement that AOS1 had agrammatic aphasia during the second assessment. There was consensus that

Table 1. Speech and language data for AOS1 and AOS2 at two points in time post–symptom onset.

Instrument	AOS1		AOS2	
	5 years	7.5 years	2 years	4 years
WAB-AQ (100)	96.6	80	93.3	93.4
Information content (10)	10	8	10	10
Fluency (10)	9	4	10	9
Auditory verbal comprehension (10)	10	10	9.45	9.8
Repetition (10)	9.3	8.6	9.6	9.0
Naming (10)	10	9.4	9.1	8.9
Writing output (WAB, Part 2) (34)	33.5	32	34	18[d]
Token Test (22)	22	19	20	20
15-item Boston Naming Test (15)	12	10	15	12
AOS Severity (0–4)[a]	2	4	1	2
Articulatory Error Score[b]	52%	63%	7%	13%
Dysarthria (0–4)[a]	0	Spastic (equivocal)	0	Spastic (equivocal)
MSD Severity (1–10)[c]	6	3	7	6
Nonverbal oral apraxia (32)	24	5	14	12

Note. AOS1 = apraxia of speech Patient 1; AOS2 = apraxia of speech Patient 2; WAB-AQ = Western Aphasia Battery Aphasia Quotient; MSD = functional speech severity rating.

[a]Severity: 0 = *normal*; 1 = *mild*; 2 = *moderate*; 3 = *marked*; 4 = *severe*. [b]Percentage of words in which an error occurred. [c]MSD severity: 1 = *nonvocal*; 3 = *speech limited to one word responses, may use nonspeech strategies for communication*; 6 = *must repeat messages on occasion*; 7 = *speech obviously and consistently impaired but remains easily understood*; 10 = *normal*. [d]This low score is an artifact of motor slowing that limited number of words produced (see transcript in text).

Table 2. Speech characteristics and prominence/severity ratings for AOS1 and AOS2 at two points in time post–symptom onset, as measured by the Apraxia of Speech Rating Scale (ASRS).

ASRS speech feature[a]	AOS1		AOS2	
	5 years	7.5 years	2 years	4 years
Distorted sound substitutions	2	3	1	1
Distorted sound additions (not including intrusive schwa)	2	3	0	0
Increased sound distortions or distorted substitutions with increased utterance length or syllable or word complexity	3	4	2	2
Increased sound distortions or distorted sound substitutions with increased speech rate	2	2	2	1
Inaccurate (off-target in place or manner) speech AMRs	0	2	0	1
Reduced words per breath group relative to maximum vowel prolongation	0	0	0	2
Syllable segmentation within words > one syllable	1	2	2	2
Syllable segmentation across words in phrases/sentences	1	2	2	2
Sound distortions	3	4	1	2
Slow overall speech rate	2	3	3	3
Lengthened vowel and/or consonant segments	1	2	2	2
Lengthened intersegment durations (between sounds, syllables, words, or phrases; possibly filled, including intrusive schwa)	1	2	1	2
Deliberate, slowly sequenced, segmented and/or distorted (including distorted substitutions) speech SMRs in comparison to speech AMRs	1	2	0	0
Audible or visible articulatory groping: speech initiation difficulty; false starts/restarts	2	3	1	1
Sound or syllable repetitions	0	0	0	0
Sound prolongations (beyond lengthened segments)	0	1	1	0
Total ASRS score	21	35	18	21
No. abnormal ASRS features	12	14	11	12

Note. AOS1 = apraxia of speech Patient 1; AOS2 = apraxia of speech Patient 2; AMR = alternating motion rates; SMR = sequential motion rates.

[a]ASRS scores: 0 = *not present*; 1 = *detectable but infrequent*; 2 = *frequent but not pervasive*; 3 = *nearly always evident but not marked in severity*; 4 = *nearly always evident and marked in severity*. The ratings reported here represent the score given by all three judges or by two of the three judges (or median rating) when agreement was not perfect.

AOS2 had equivocal evidence of aphasia during the second assessment. Any aphasia was clearly less severe than AOS in both cases.

Temporal Acoustic Measures

Responses to several supplementary speech task items were measured acoustically to quantify some temporal characteristics relevant to AOS. Measures included (a) three repetitions each of the words *cat*, *catnip*, *catapult*, and *catastrophe*; (b) a single repetition of the sentence, "The municipal judge sentenced the criminal"; (c) speechlike AMRs (rapid repetitions for /pʌ/, /tʌ/, and /kʌ/); and (d) speechlike SMRs (rapid repetitions of /pʌtʌkʌ/). It was hypothesized that the AOS cases would have abnormally long durations, consistent with the slow rate that is characteristic of AOS in general and, furthermore, that the abnormal durations would be greater for longer than shorter utterances because AOS is negatively influenced by increased utterance length or complexity (Haley & Overton, 2001; Strand & McNeil, 1996). It was also hypothesized that syllables per second for all participants would be greater for AMRs than multisyllabic words and sentences because AMRs are maximum rate performance tasks likely guided by motor processes that differ from those for multisyllabic word and sentence utterances, which have greater programming demands (Ziegler & Wessel, 1996). Word and sentence repetitions had no rate requirements, and stimuli were delivered at a normal rate. Similarly, it was hypothesized that AMRs would be more rapid than SMRs because of increased phonological or motor planning/programming demands for SMRs.

The duration of each word and sentence was measured from the release of the initial stop or the initial onset of noise energy or voicing for each word or the sentence to cessation of acoustic energy at the end of the word or sentence. The duration of each word reported here represents the average duration of the three repetitions. Syllables per second for the repeated words and the sentence were derived by dividing the number of syllables in the word or sentence by its duration.

AMR data reflect the average syllable rate per second across /pʌ/, /tʌ/, and /kʌ/ on the basis of the first 10 consecutive successful repetitions (or the maximum number produced if fewer than 10) of each syllable. SMR data reflect the syllable rate per second across the total duration of the first three successful consecutive repetitions of /pʌtʌkʌ/ (i.e., a total of nine syllables).

Finally, to quantify abnormal syllabic stress and related segmentation of syllables commonly associated with AOS (Kent & Rosenbek, 1983; Odell, McNeil, Rosenbek, & Hunter, 1991; Strand & McNeil, 1996; Ziegler, 2002), a pairwise variability index (PVI), a measure of the degree of equalized syllabic stress, was computed from the first and second syllables in the three-syllable word *catastrophe* (averaged over the three consecutive productions). The PVI formula used was $PVI = 100 \times (d1 - d2) / [(d1 + d2) / 2]$, where d is duration of the first or second vowel in a word of two or more syllables (Ballard et al., 2014; Vergis et al., 2014). PVI values closer to zero are consistent with more equalized stress between compared syllables/vowels. For the stimulus, *catastrophe*, PVI values should be negative because the first syllable is unstressed (shorter) and the second syllable is stressed (longer). It was hypothesized that AOS1 and AOS2 would maintain the stress distinction between the two syllables but that the distinction would be less than that achieved by control participants. This hypothesis is supported by findings for individuals with stroke-related AOS and the nonfluent variant of PPA with frequent co-occurring AOS (Ballard et al., 2014; Vergis et al., 2014).

Control participants for acoustic comparisons. Thirteen individuals (six women, seven men) without evidence of AOS or dysarthria, ranging in age from 50 to 80 years ($M = 63.1$ years), served as controls for the acoustic comparisons. Four had no evidence of aphasia; they were seen as part of the routine speech-language pathology clinical practice. The remaining nine participants were part of the study that included AOS1 and AOS2. Four of the nine had language complaints, but comprehensive speech-language assessment failed to reveal evidence of aphasia or a motor speech disorder; clinical neurological assessment and neuroimaging results were also normal. The remaining five individuals had no evidence of AOS or dysarthria but did have mild PPA. Thus, none of the 13 control participants had evidence of any motor speech disorder, but five had mild aphasia.

The inclusion of individuals with mild aphasia might suggest that the control data would be more stringent for detecting temporal abnormalities associated with PPAOS than if only individuals without neurologic disease or aphasia were included. However, after dividing the control participants into two subgroups, one containing the eight participants without aphasia and the other containing the five participants with mild aphasia, *t* test comparisons failed to identify statistically significant differences ($p > .05$) between the subgroups for any of the acoustic measures reported here. Thus, the two subgroups were combined into a single control group. The speech analysis software Praat (version 5.3.63; Boersma & Weenink, 2014) was used for all acoustic measures.

Reliability of acoustic measures. Two of the authors (J.R.D., H.C.) independently measured the indices reported here for both cases on both test occasions and for three randomly selected CONTROL participants. All correlations between the two judges across the seven data sets exceeded .99, and no between-judges *t* test comparison for any of the data sets was significant ($p > .05$). Differences in raw data measurements between the two judges averaged less than 2% and ranged from 0.3% to 5.8% across the seven data sets. Therefore, the reliability of the temporal measures was considered good. Across the entire data set, the 8% of comparisons that differed by more than 5% were remeasured to yield a consensus measure.

Only two responses from control participants could not be measured validly (false start, poor retention of sentence stimulus). Five percent of the responses for the two patients with AOS could not be measured validly because of false starts/restarts, distorted sound additions, or giving

up on an attempted response. Computed averages were adjusted accordingly.

Results

Speech-language findings for both individuals at each time point are summarized in Table 1. ASRS ratings are summarized in Table 2 and acoustic measures in Table 3 and Figures 1 and 2.

Case AOS1—Time 1

AOS1, a 49-year-old right-handed man, first presented for neurological examination with a 6-month history of difficulty "getting the words out right." He had no history or recent complaints of language difficulty. He was working full time in a sales position. Speech-language assessment yielded no evidence of aphasia or dysarthria. His speech characteristics were consistent with mild AOS. Clinical neurological examination was otherwise entirely normal. Positron emission tomography and cerebrospinal fluid studies were normal.

He was seen yearly for the next 3 years, during which his speech difficulty gradually worsened without new neurological symptoms. Because of his speech problem, he had left his sales job to take a position screening and welcoming visitors at a prison, but he was considering applying for disability because of speech-related stress at work. Speech-language examinations confirmed progression of his AOS and failed to detect any aphasia or dysarthria. The neurologic diagnosis on each occasion was PPAOS.

AOS1 entered the research study at age 53 years, about 5 years postonset, noting that his speech difficulty continued to progress and that it had led to anxiety and depression for which he was taking anti-anxiety and antidepressant medications with benefit.

Language. He achieved a WAB-AQ of 96.6 (normal). His Token Test score and WAB Writing Output were normal. His score of 12 on the 15-item Boston Naming Test was borderline normal, but there was no obvious anomia during conversation or during any other spoken language task. The following excerpts from his spoken and written descriptions of the WAB "picnic scene" illustrate the adequacy of his narrative language:

> [Spoken] "Well, the young boy's flyin' a kite. His dog is running behind him. There's a girl on the beach makin' a sand castle."
> [Written] "There's a young couple having a pictic [sic] while a young boy is flying a kite and running his dog. There is a man fishing off the dock and a young girl is making a sand castle."

Speech. During WAB speech subtests, his prosody was abnormal (mildly slow rate, occasional syllable or word segmentation). He had multiple articulatory errors, similar to those made during the supplementary speech tasks, during which he exhibited distorted substitutions, groping, false starts, additions, repetitions, prolongations, or omissions on 23 of 39 word repetition items and six of 17 of words in three sentences, for a total Articulatory Error Score of 52%. Speech AMRs and SMRs were produced without articulatory errors beyond mild distortions. His overall score of 21 on the ASRS was in the abnormal range (Josephs et al., 2012; Strand et al., 2014), with abnormalities noted on 12 of the 16 items. Six of the seven most prominent abnormalities (ratings of 2 or 3) reflected articulatory difficulties (distorted

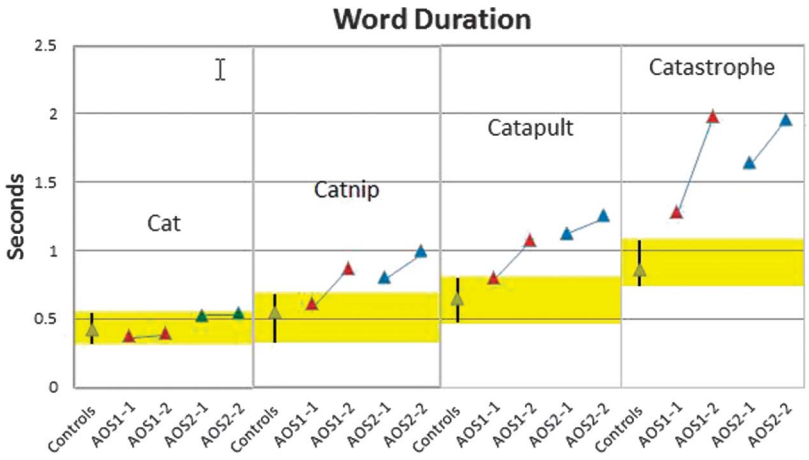
Table 3. Summary of acoustic temporal measures.

Measure	Controls[a]	AOS1		AOS2	
		5 years	7.5 years	2 years	4 years
Duration (seconds)					
Cat	0.423 (0.318–0.540)	0.381	0.402	0.526	0.545
Catnip	0.550 (0.326–0.683)	0.613	0.870[c]	0.806[c]	1.001[c]
Catapult	0.650 (0.478–0.795)	0.800[c]	1.075[c]	1.127[c]	1.260[c]
Catastrophe	0.862 (0.743–1.076)	1.287[c]	1.986[c]	1.646[c]	1.961[c]
The municipal...	2.773 (2.115–4.500)	4.386	X[€]	6.524[c]	7.24[c]
Syllables per second					
Cat	2.37 (1.76–3.14)	2.62	2.49	1.90	1.83
Catnip	3.64 (2.93–6.13)	3.26	2.30[c]	2.80[c]	2.12[c]
Catapult	4.62 (3.77–6.28)	3.75 [γ]	2.79[c]	2.85[c]	2.38[c]
Catastrophe	4.64 (3.72–5.38)	3.11 [γ]	2.01[c]	2.53[c]	2.04[c]
The municipal...[b]	4.50 (2.67–5.67)	4.38	X[d]	1.84[c]	1.66[c]
AMR	6.21 (5.19–7.28)	4.37 [γ]	2.92[c]	2.21[c]	2.21[c]
SMR	4.54 (2.71–6.26)	3.74	3.09[c]	2.38[c]	2.36[c]
Pairwise Variability Index					
Catastrophe	–90.5 (–38.0–163.7)	–54.2[c]	–28.7[c]	–27.5[c]	–42.2[c]

Note. AOS1 = apraxia of speech Patient 1; AOS2 = apraxia of speech Patient 2; AMR = alternating motion rates; SMR = sequential motion rates.

[a]Mean (range) for 13 control speakers. [b]"The municipal judge sentenced the criminal" (12 syllables). [c]Outside control range. [d]Could not be measured validly.

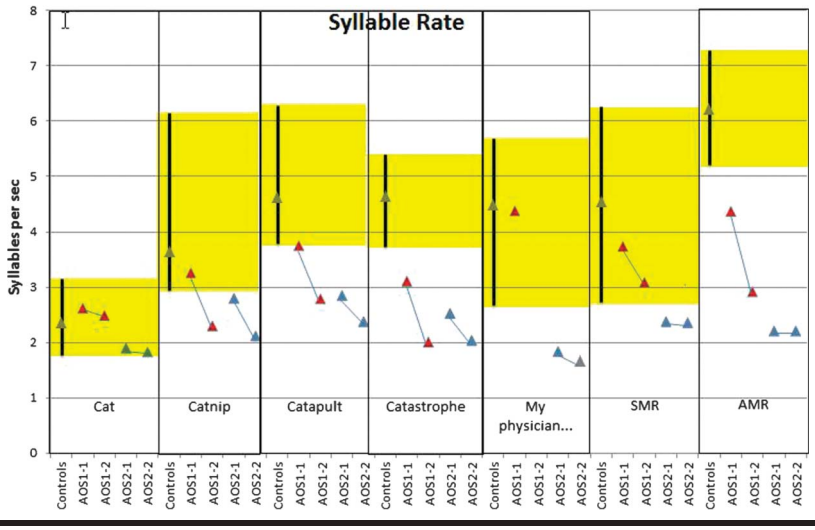
Figure 1. Mean word durations for control participants (vertical bar and shading represents range of durations) and AOS1 and AOS2 at two points in time.



sound substitutions; distorted sound additions; increased distortions or distorted substitutions with increased length or complexity; increased distortions or distorted substitutions with increased speech rate; sound distortions, audible or visible articulatory groping, speech initiation difficulty, or false starts/restarts). Rate and prosodic abnormalities were also evident but generally less prominent. There was no evidence of dysarthria. The clinical rating of AOS severity was 2 (*moderate*) and the global motor speech rating was 6 (*must repeat messages on occasion*). Performance on the measure of nonverbal oral apraxia was mildly impaired (groping and off-target movements when attempting to click his tongue on two trials, including on imitation).

Acoustic measures. Duration for the multisyllabic word, *catastrophe*, was clearly slower than normal. The duration of the measured sentence was within the control range. Syllables per second were marginally slower or clearly slower than normal for the three- and four-syllable word stimuli, respectively. AMRs were slow. SMRs were slower than AMRs (as they were for controls), but they fell within the control range. Finally, the PVI of −54.2, although consistent with appropriate stress distinction, was attenuated (i.e., closer to zero) relative to the control mean (−90.5) and all but one control participant who had a PVI of −38.0; all other control participants had PVIs greater than −60.0. Although vowel durations within the initial unstressed syllable and the following stressed syllable were both abnormally lengthened, the initial unstressed syllable vowel was disproportionately lengthened (2.3 times greater than the control group mean) compared with the stressed syllable

Figure 2. Syllable rate per second for words of increasing length, sentence, and speech sequential motion rates and alternating motion rates for control participants (vertical bar and shading represents range of durations) and AOS1 and AOS2 at two points in time.



vowel (1.6 times greater than the control group mean). This PVI attenuation is consistent with relative equalization of stress due more to increased stress on unstressed than stressed syllables.

Neurological findings. There were no motor or sensory deficits suggestive of neurodegenerative diseases such as progressive supranuclear palsy or corticobasal syndrome. His examination was completely normal except for a slight reduction of left arm swing and slight slowing of rapid alternating finger movements on his left hand. Performance on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), a global measure of cognitive function, was normal. Fluorodeoxyglucose-positron emission tomography (FDG-PET) showed subtle hypometabolism in the supplementary motor area, posterior lateral frontal lobes, and caudate nucleus. Atrophy on magnetic resonance imaging (MRI) was observed in the posterior lateral frontal lobes and insula, involving the left hemisphere to a greater degree than the right, and the supplementary motor area.

Case AOS1—Time 2

AOS1 was seen for reassessment at age 56 years, 7.5 years postonset. Compared with Time 1, his signs and symptoms had clearly progressed.

Language. Aphasia was now evident. His WAB AQ had fallen to 80 (mild-moderate impairment). He had mild confrontation naming and equivocal verbal comprehension difficulty. There was evidence of mild agrammatism, as reflected in his WAB Fluency score of 4 and as exemplified in the following excerpts from his WAB picnic scene descriptions:

> [Spoken] "Boy flyin' a kite. Sailboat in the water. Car in the driveway." (This transcription required some inference due to reduced intelligibility. Several additional utterances were unintelligible.)
> [Written] "Gal and guy are having a picnic. The boy and his dog are flying a kite. The house is got a flag flying in the yard. The driveway of the house is car on it."

Speech. Prosody had worsened (e.g., slower rate, more prominent syllable segmentation), but his articulatory errors had become even more prominent (several ratings of 3 or 4). His overall ASRS score was unambiguously worse (35 versus 21 at Time 1); 11 of the 12 features rated as abnormal at Time 1 were judged as more evident or severe. AMRs were now sometimes off-target in place or manner, and sound prolongations were now occasionally evident. On the supplementary speech tasks, he exhibited distorted substitutions, groping, false starts, additions, repetitions, prolongations, and/or omissions on 27 of 39 word repetition items and eight of 17 words in three sentences for a total Articulatory Error Score of 63%. His overall AOS severity was rated 4 (*severe*), and his MSD severity was rated 3 (*intelligible speech limited to one-word responses*). Spastic dysarthria was, by consensus, judged as equivocally present, primarily on the basis of strained or equivocally strained voice quality, a feature not associated with AOS.

Acoustic measures. All word duration and syllable per second measures were slower than at Time 1; two- to four-syllable words were produced 26% to 35% more slowly at Time 2 than Time 1. Sentence duration could not be measured validly because of false starts, prolonged hesitations, and distorted sound additions. AMRs and SMRs had noticeably slowed, but AMRs were slowed to a greater degree. Time 2 AMRs were 33% slower than at Time 1; Time 2 SMRs were 17% slower. The PVI measure now was clearly abnormal; similar to Time 1, the initial unstressed and following stressed vowels were both lengthened compared with controls, but the initial unstressed vowel was disproportionately lengthened (5.2 times greater than the control mean) compared with the following stressed vowel (2.7 times greater than the control mean).

Neurological findings. Once again, there were no motor or sensory deficits suggestive of any other neurodegenerative disease. Rapid alternating finger and hand movements were again mildly slowed and again it was noted that he had reduced left arm swing with ambulation. The global measure of cognitive function (MMSE) was in the normal range. FDG-PET and MRI showed slight progression in regions of abnormality noted at baseline. Progressive brain atrophy was observed over time with a rate of whole brain atrophy of 1.1% per year. This rate is similar to the median rate of 1.5% (range = 0.6% to 3.0%) per year for a group of patients with PPAOS and greater than the median rate of 0.4% (range = −0.3% to 1.1%) per year that is observed in healthy control subjects (Josephs et al., 2014).

Case AOS2—Time 1

AOS2, a 73-year-old right-handed woman, first presented for neurological examination with a chief complaint of insidious onset speech difficulty of about two years duration. She had no prior history of speech, language, or neurological problems. She had no memory complaints and was independent in activities of daily living, including managing her finances. She denied problems with spoken or written language comprehension, writing, or spelling. She denied difficulty with word retrieval but admitted to occasionally substituting yes for no or vice versa (see Frattali, Duffy, Litvan, Patsalides, & Grafman, 2003, for information about yes/no substitutions that can occur independent of aphasia).

The evaluating speech-language pathologist concluded that she had mild AOS without any accompanying aphasia or dysarthria. Neurological examination noted her speech difficulty as well as upper limb apraxia. She did not meet diagnostic criteria for progressive supranuclear palsy syndrome, corticobasal syndrome, or multiple system atrophy. The neurologic diagnosis was descriptive of her symptoms, which included predominant progressive AOS. AOS2 entered the research study about three months later, just over 2 years post symptom onset. Speech difficulty remained her chief complaint.

Language. She achieved a WAB-AQ of 93.3, just below the cutoff for normal performance. Her somewhat reduced WAB Naming score (9.1) was attributed to reduced Animal Fluency performance (score of 11), a word-generation task that is frequently reduced in people with PPAOS in the absence of other evidence of anomia (Josephs et al., 2012); given the absence of anomia or other evidence of aphasia on other language tasks, it is likely that her reduced word fluency score reflected reduced sustained attention or slowed processing speed. Performance on the Token Test, Boston Naming Test, and WAB Writing Output subtest was normal. The conclusion by the examining clinician and during consensus discussion was that aphasia was not present. The following excerpts from her spoken and written descriptions of the WAB picnic scene illustrate the adequacy of her narrative language:

> [Spoken] "I see mom and dad having a picnic and relaxing. She's pouring a drink of wine and listening to the radio and he's reading a story. The boy is flying a kite and the dog is following him."
> [Written] "The mom and dad are on a picnic blanket. The mom is pouring a drink. The boy is flying kite. The girl is making a sandcastle in the sand."

Speech. During the WAB picture description and repetition subtests, speaking rate was consistently slow, with intersyllable and interword segmentation. Mild articulatory distortions were evident, but she had only a few distorted substitutions, false starts, or sound prolongations. On the supplementary speech tasks, distorted substitutions, sound prolongations, or false starts occurred on only three of 39 word repetition items and one of 17 words in the repeated sentences, for a total Articulatory Error Score of 7%. Speech AMRs and SMRs were slow but without articulatory errors beyond mild distortions. Her overall ASRS score was clearly in the abnormal range, with abnormality noted on 11 of the 16 items; four of her six most prominent abnormalities (ratings of 2 or 3) were related to rate and prosody. There was no evidence of dysarthria. The clinical rating of AOS severity was 1 (*mild*) and the global motor speech rating was 7 (*easily understood*). Performance on the measure of nonverbal oral apraxia was moderately impaired, reflecting inaccurate responses to command or ultimately accurate responses but with delays or groping responses.

Acoustic measures. Durations for all two- to four-syllable words and the sentence were longer than normal. Syllables per second were normal for *cat* but slower than normal for all other stimuli, including AMRs and SMRs. AMR and SMR rates were not substantially different from one another. In fact, the syllable rate was fairly stable across all of the measured responses, generally in the range of two to three syllables per second. Finally, the PVI measure, although consistent with appropriate stress distinction, was attenuated relative to control data, consistent with relative equalization of stress. Although the vowel durations within the initial unstressed and following stressed vowel were both lengthened compared with controls, the initial unstressed vowel was disproportionately lengthened (4.6 times greater than the control mean) compared with the following stressed vowel (2.6 times greater than the control mean).

Neurological findings. Performance of the MMSE was normal. There was evidence of mild parkinsonism, which was characterized by reduced right arm swing with ambulation; mildly increased tone in the right arm; and mildly slowed alternating motor rate in the right fingers, hand, and leg, more so than on the left. Saccadic upward-gaze eye movement was marginally slow. Ideational apraxia was evident on complex upper limb tasks requiring sequential arm movements. FDG-PET showed posterior lateral frontal lobe, supplementary motor area, and caudate nucleus and midbrain hypometabolism, with left greater than right hemisphere involvement. On the MRI, atrophy was observed in the supplementary motor area, caudate nucleus, and putamen, more so in the left than right hemisphere, as well as the midbrain.

Case AOS2—Time 2

AOS2 was seen for reassessment at age 75, about four years postonset. She and her husband felt her speech had slowed and that her writing had progressively worsened. She had balance difficulty with occasional falls, shuffling gait, and reduced arm swing, difficulty arising from a chair, problems turning in bed, and swallowing difficulty.

Language. Her language scores had changed minimally, but there was equivocal evidence of aphasia, primarily on the basis of her Boston Naming Test score, which had fallen into the borderline abnormal range, although anomia was not obvious during conversational or narrative language. Her low score on the WAB Writing Output subtest was predominantly or exclusively an artifact of motoric slowing that limited the number of words written within the 3-min time limit for the task. The following brief excerpts of her spoken and written WAB picnic scene descriptions illustrate the adequacy of her language expression:

> [Spoken] "The man is reading and the lady is getting ready for a picnic and pouring pop or wine for him. And the boy is, um, flying a kite. And the man is fishing and caught a fish."
> [Written (full transcription)] "The man is reading a book. The woman is pouring the wine. The boy is flying a kite."

Speech. Perceptual ratings of speech were consistent with mild worsening of AOS. During the WAB picture description and repetition subtests, her slow rate and segmentation were somewhat worse, but articulatory characteristics were relatively unchanged. On the supplementary speech tasks she had some consonant omissions (or reduced audibility of their production) or false starts or self-correction of articulatory errors on six of 39 word repetition items and one of 17 distorted substitutions in the three repeated sentences, for a total Articulatory Error Score of 13%. Her score on the ASRS was only slightly worse, with only one additional feature not noted during the initial evaluation

(reduced words per breath group relative to maximum vowel prolongation). Overall AOS severity, initially judged as mild, was now judged as moderate, and the global motor speech rating had dropped 1 point, from 7 to 6 (*must repeat messages on occasion*). There was consensus that spastic dysarthria was equivocally present, primarily on the basis of equivocal-to-mild strained voice quality, a feature not associated with AOS.

Acoustic measures. All word duration and word syllable per second measures were slower than at Time 1; two- to four-syllable words were produced 11% to 19% more slowly at Time 2 than Time 1, and sentence duration was 10% slower at Time 2 than Time 1. AMRs and SMRs remained very slow but were unchanged. The PVI measure was somewhat better but remained lower than that for all but one control participant; there was still disproportionate lengthening of the vowel within the initial unstressed syllable (5.1 times greater than the control mean) compared with the vowel within the following stressed vowel (3.1 times greater than the control mean).

Neurological findings. Neurologic examination was unequivocally worse, revealing moderate parkinsonism, absent vertical eye movements, right upper limb dystonic posturing, and severe right greater than left limb apraxia. There was no tremor or tremulousness. Performance on the MMSE was again normal. There were no signs of behavioral dyscontrol. It was felt that she now had features that overlap with progressive supranuclear palsy syndrome and corticobasal syndrome, perhaps predominantly the former. FDG-PET showed slight progression of hypometabolism in the same regions noted during initial evaluation. MRI revealed progression of atrophy at a rate of whole brain atrophy of 1.5% per year.

Discussion

The cases presented here illustrate that AOS can be the initial manifestation of neurodegenerative disease, that it can occur without aphasia or dysarthria, and that it can be the only or predominant neurological sign for an extended time. AOS1 had no aphasia or dysarthria at 5 years postonset, and when aphasia and equivocal dysarthria were evident at more than seven years the AOS remained the primary communication problem. There was only equivocal evidence of aphasia and dysarthria in AOS2 when she was last seen at 4 years postonset. These time-from-onset durations for isolated AOS are within the duration range for a cohort of people we have followed with PPAOS that includes these two patients, in which median duration at initial evaluation was 3 years, with a range of 1.4 to 6 years (Josephs et al., 2012, 2014). Neuroimaging abnormalities for both cases included regions associated with speech motor programming and planning and are compatible with those reported for PPAOS (Josephs et al., 2010, 2012, 2013, 2014; Laganaro et al., 2012). These data justify recognition of PPAOS as a distinct clinical entity that should not be subsumed under the heading of PPA.

There was evidence of AOS progression over a 2- to 2.5-year period in both cases. The ASRS captured changes in specific AOS characteristics, and other clinical ratings captured more global severity changes. Progression was also clearly evident in most of the acoustic measures. In addition, AOS1 developed problems consistent with agrammatic aphasia, in which AOS occurs with high frequency, especially when the predominant AOS features are articulatory as opposed to prosodic in nature (Josephs et al., 2013). Equivocal evidence of aphasia emerged in AOS2, but an aphasia subtype could not be determined with confidence. Equivocal spastic dysarthria emerged in both cases, which is consistent with the bilateral abnormalities that were evident on neuroimaging (Clark et al., 2013). And, in AOS2, neurologic examination at 4 years detected clinical features consistent with progressive supranuclear palsy syndrome and corticobasal syndrome. In spite of the emergence of these additional problems, in both cases AOS remained the predominant communication disorder. As already noted, the most frequent pathological diagnoses at autopsy for people with PPAOS as well as PPA with AOS are progressive supranuclear palsy or corticobasal degeneration, hence underlying tau pathology. Recognition of this association with underlying pathology may become very important for early intervention with pharmacologic treatments when they become available and for future genetic studies (Duffy & Josephs, 2012; Josephs et al., 2013).

In both cases, the characteristics of the AOS were similar to the perceptual features of stroke-induced AOS. These characteristics were reflected in ASRS ratings, which include features considered unique to AOS as well as features that can overlap with aphasia and dysarthria. The absence of aphasia or dysarthria in both cases, at least at the time of initial evaluation, suggest that their ASRS scores represented a reasonable quantified index of the prominence and severity of AOS that was related to more global ratings of clinical severity and was sensitive to progression over time. The ASRS requires further development as a standard clinical measure, but, in response to calls for operationalized clinical metrics (e.g., Haley et al., 2012), it shows promise as a quantifiable measure of AOS (Strand et al., 2014).

Similarly, the Articulatory Error Score served to quantify the frequency with which articulatory errors occurred during repetition of specific spoken stimuli. It seemed sensitive to increased articulatory difficulty over time in both cases and, along with the acoustic measures, helped to quantify differences in the pattern of difficulty between the two cases. That is, AOS1 had considerably higher Articulatory Error Scores than AOS2 during both assessments (52% and 63% versus 7% and 13%, respectively), whereas AOS2 had longer word and sentence duration and reduced syllables per second compared with AOS1. These different profiles raise the possibility that the articulatory as opposed to prosodic features typically associated with AOS may not reflect identical planning or programming deficits. These differences are relevant to recent findings by Josephs et al. (2013),

on the basis of clinical judgments, that some people with PPAOS have a profile of difficulty dominated by articulatory errors, whereas others have predominant problems with rate and syllable segmentation. The former pattern was more likely to occur in people with agrammatic aphasia that was more severe than AOS, whereas the latter pattern was more likely in people with PPAOS or AOS that was more severe than any aphasia; a third pattern was evident in which there was no obvious difference in the prominence of articulatory versus rate and syllable segmentation deficits, a pattern that, in our experience, is likely very typical in stroke-induced AOS. The simple metrics described here for quantifying articulatory versus rate/segmentation deficits may represent a useful way to quantify such differences in future studies of neurodegenerative and stroke-induced AOS, including efforts to determine how PPAOS may or may not be different from stroke-induced AOS.

Regarding the simple acoustic measures reported here, findings for both cases are consistent with hypotheses that they would have abnormally long word and sentence durations and reduced syllables per second during speech and speechlike tasks (AMRs and SMRs) and that those abnormalities would be greater for longer than shorter utterances, consistent with findings for stroke-induced AOS (Haley & Overton, 2001; Liss & Weismer, 1994; Strand & McNeil, 1996). This is also compatible with the inference that challenges to speech planning (e.g., reduced access to motor plans) slows "delivery" of syllables and lengthens utterance durations (Laganaro et al., 2012; Ziegler, 2002). The hypothesis that syllables per second would be greater for AMRs than multisyllabic words and sentences was partly supported for AOS1 at Time 1, in that his AMRs were more rapid than any of the four words and SMRs, but they were not more rapid than his sentence syllable rate. At Time 2 his AMRs had slowed more dramatically than any of the other stimuli but nonetheless remained somewhat more rapid than three of the four words, but not SMRs. For AOS2, the results ran counter to the hypothesis. In general, her AMRs were slower compared with most of the other stimuli, including SMRs. The inability to increase rate on the maximum performance AMR task argues against the notion that slow rate in AOS, at least in this case, reflects a compensatory strategy rather than a primary feature of the disorder (cf. Laganaro et al., 2012; McNeil, Caliguiri, Weismer, & Rosenbek, 1986; Rogers, 1997). Uniformly slow syllables per second and their restricted range across stimuli (about 2 to 3 per second) suggests a pervasive slowing of speaking rate regardless of task complexity or rate requirements. This could reflect a severity "floor effect" in which task complexity was no longer sensitive to gradations in motor planning and programming demands. Alternatively, it could represent the effects of slowed neuromuscular execution as might occur in dysarthria, although dysarthria was not evident at Time 1 and only equivocally evident at Time 2 for both cases; we also cannot rule out the possible influence of aphasia on some of the temporal measures at Time 2 for both cases. Studies of larger numbers of people with PPAOS and comparisons with people with dysarthria but no AOS and with PPA but no AOS may help clarify these issues (cf. Ziegler & Wessel, 1996). Although the acoustic measures reported here were clearly sensitive to AOS in these two cases, additional studies will need to establish the degree to which they are specific to PPAOS when compared with dysarthrias, particularly spastic and ataxic dysarthria, which share several perceptual features with AOS, and to the phonologic errors that can occur frequently in some people with PPA (Ballard et al., 2014; Petroi, Duffy, Strand, & Josephs, 2014; Ziegler, 2002).

The reduced PVI values for both cases at both points in time are consistent with observations of equalized stress in AOS in general (Kent & Rosenbek, 1983; Odell et al., 1991). They also support the suggestion that acoustic temporal contrasts, such as between stressed and unstressed syllables, have the potential to reveal abnormalities associated with and perhaps unique to AOS (Ballard et al., 2014; Rogers, 1997). For both patients, at both test times their PVI values were consistent with appropriate linguistic stress contrast but considerably less than the control group mean and consistently less than the PVI for all but one of the control participants. This is consistent with recent findings of Ballard et al. (2014) that PVI using vowel duration was useful in discriminating progressive AOS (with agrammatic aphasia) from control subjects and individuals with the logopenic variant of PPA. Obviously, further study is necessary to determine whether PVI alone, among acoustic temporal measures, can reliably make such diagnostic distinctions, or whether some combination of several acoustic and quantified perceptual measures is required to maximize diagnostic accuracy and specificity (cf. Haley et al., 2012).

In summary, the two cases presented here are representative of PPAOS, a recognizable clinical entity that is often buried within the syndrome of PPA. PPAOS is distinguishable in its clinical presentation, salient clinical characteristics, and clinical neurological and neuroimaging findings from other neurodegenerative speech and language disorders. Its features and their relative prominence can be captured with a rating scale of speech features associated with AOS and further quantified with a relatively simple measure of articulatory errors and several easy-to-measure acoustic temporal features. These approaches to quantifying the features of PPAOS, and perhaps AOS regardless of etiology, require further refinement, but they, or their variants, have potential as quantifiable indices for differential diagnosis, severity, and change over time. They may also contribute to our understanding of similarities and differences between neurodegenerative versus stroke-induced AOS and the possible existence of AOS subtypes.

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Appendix

Supplementary Speech Tasks

1. "Take a deep breath and say 'ah' for as long and steadily as you can" (clinician provides model).

2. "Take a breath and repeat 'puhpuhpuh' as fast and as steadily as you can. Keep it up for a while." Do the same for 'tuh' and 'kuh.' Strive for a minimum of 10 repetitions; clinician provides model.

3. "Take a breath and repeat 'puhtuhkuh' as fast and as steadily as you can. Keep it up for a while." Strive for a minimum of three repetitions of the sequence; clinician provides model.

4. "Repeat each of the following words three times each." No requirement regarding speed; clinician provides a model using the word *boy*. Repeat stimulus once and allow a second trial of an item if patient produces a semantic error; adds or omits sounds or syllables; or repeats or revises sounds, syllables, or words.

Cat	Catnip	Catapult	Catastrophe	Harmonica
Specific	Snowman	Artillery	Statistics	
Stethoscope	Aluminum	Rhinoceros	Volcano	

5. "Repeat these sentences one time." No requirement regarding speed; clinician provides model at normal rate; repeat stimulus once if patient fails to retain the stimulus; produces a semantic error; adds or omits sounds or syllables; or repeats or revises sounds, syllables, or words.

   a. We saw several wild animals.

   b. My physician wrote out a prescription.

   c. The municipal judge sentenced the criminal.